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| EXAMINER |
|---|
| SAOUD, CHRISTINE J |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1647 | |

DATE MAILED: 10/02/2002 13

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/904,485 | ASHKENAZI et al. |
| **Examiner** | **Art Unit** |
| Christine Saoud | 1647 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) ☐ Responsive to communication(s) filed on _____ .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) ☒ Claim(s) 39-51 is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 39-51 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5,8
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other.

## DETAILED ACTION

### *Response to Amendment*

1. Claims 1-38 have been canceled and claims 39-51 have been added as requested in the amendment of paper #12, filed 13 July 2001. Claims 39-51 are pending in the instant application.

### *Priority*

2. According to the priority statement of 26 August 2002, it appears that the claimed subject matter defined in the instant application is supported by PCT application PCT/US00/04414 filed 2/22/2000. Based on the invention given by Applicant and an inspection of the patent applications, the Examiner has concluded that the subject matter defined in this application is supported by the disclosure PCT/US00/04414, filed 2/22/2000 but is not supported by any of the other applications because the claimed subject matter does not have utility/enablement. The use of the claimed invention for inhibition of VEGF stimulated proliferation of adrenal cortical capillary endothelial cells is first taught in PCT/US00/04414, and this is found to have utility and is enabled by the specification as filed. However, PCT/US98/19437, filed 9/17/1998 does not teach this utility, and therefore, priority is not granted to this application. Accordingly, the subject matter defined in claims 39-51 has an effective filing date of 2/22/2000.

Should the Applicant disagree with the Examiner's factual determination above, it is incumbent upon the Applicant to provide the serial number and specific page number(s) of any parent application filed prior to 2/22/2000 which specifically supports the particular claim

limitation for each and every claim limitation in all the pending claims which Applicant considers to have been in possession of and fully enabled for prior to 2/22/2000.

***Specification***

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See page 124, line 37. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

***Claim Rejections - 35 USC § 112***

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 39-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The protein identified as PRO217 is a soluble protein, and is not disclosed as being expressed on a cell surface. Accordingly, the imitation that the claimed protein comprises an "extracellular domain" (for example, see claim 39, parts (c) and (d)) is indefinite, as the art does not recognize soluble proteins as having such domains. Further, if the protein had an extracellular domain, the recitation of "the extracellular domain" ... "lacking its associated signal sequence" (claim 39, part (d), for example) is indefinite as a signal sequence is not generally considered to be

part of an extracellular domain, as signal sequences are cleaved from said domains in the process of secretion from the cell.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 39-43, 50-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated polypeptide having at least 80% amino acid sequence identity to the polypeptide of SEQ ID NO:4 or the mature form thereof, which isolated polypeptide inhibits VEGF stimulated proliferation of adrenal cortical capillary endothelial cells, does not reasonably provide enablement for a polypeptide not identical to at least the mature form of SEQ ID NO:4 which does not have this activity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. In re Wands, 858, F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to a polypeptide having at least 80% amino acid sequence identity to the polypeptide of SEQ ID NO:4 or the extracellular domain thereof, both referred to as PRO217. There is no functional limitation in the claims. Applicant has taught the polypeptide of SEQ ID NO:4, the mature form thereof and a putative signal sequence. This polypeptide was shown to inhibit VEGF stimulated proliferation of adrenal cortical capillary endothelial cells (pages 204-205, Example 66).

The claim encompasses an unreasonable number of inoperative polypeptides, which the skilled artisan would not know how to use. While the specification suggests that the polypeptide of SEQ ID NO:4 is related to EGF, what receptor it binds or what EGF-related function it possesses aside from inhibiting VEGF stimulated proliferation of adrenal cortical capillary endothelial cells is undisclosed. Since PRO217 is a secreted protein, it would be expected that the mature form would be sufficient for function in the absence of the secretory signal. The function domain of an EGF molecule is the mature form. As opposed to the claims, what is disclosed about PRO217 is narrow: a single polypeptide with one disclosed function and no other obvious specific functions. The prior art does teach a polypeptide with the amino acid sequence of SEQ ID NO:4, called WIF-1 (HSIEH et al. Nature 398: 431-436, 1999), but the instant specification does not recognize properties of the polypeptide except as a inhibitor of VEGF stimulated proliferation of adrenal cortical capillary endothelial cells. The skill in the EGF art is not high because there are several classes of proteins within the EGF "family", and there is great diversity of function (Carpenter et al. Handbook of Experimental Pharmacology; Chapter 4, The

Epidermal Growth Factor Family, pages 69-171, 1990). Therefore, knowledge of one EGF-like protein's structure and function does not provide predictability about function of a structurally related EGF protein, even within the same class.

There are no working examples of polypeptides less than 100% identical to the polypeptide of SEQ ID NO:4 or the mature form thereof. There are several functions attributed to PRO217 (see Examples 66, 69, 74, and 77). The results of Examples 69, 74 and 77 do not provide the skilled artisan with guidance for how to use the polypeptide; the results of Example 66 do. The skilled artisan would not know how to use non-identical polypeptides on the basis of teachings in the prior art or specification unless they possessed the function of inhibiting VEGF stimulated proliferation of adrenal cortical capillary endothelial cells disclosed in the instant specification. While the specification generally described properties of EGF molecules, it is acknowledged that EGF molecules are diverse in function and structure (pages 2-3 of the specification and Carpenter et al.). The specification does not provide guidance for using polypeptide related to (i.e., 80%-99% identity) but not identical to SEQ ID NO:4 which do not have the activity of inhibiting VEGF stimulated proliferation of adrenal cortical capillary endothelial cells. The claims are brad because they do not require the claimed polypeptide to be identical to the disclosed sequence and because the claims have no functional limitation.

For these reasons, which include the complexity and unpredictability of the nature of the invention and are in terms of the diversity of EGF-like molecules and the lack of knowledge about function(s) of encompassed polypeptides structurally related to PRO217 having the amino acid

sequence of SEQ ID NO:4, the one limited working example of PRO217 and its one enabled function, the lack of direction or guidance for using polypeptides that are not identical to at least the extracellular domain of SEQ ID NO:4, and the breadth of the claims for structure without function, it would require undue experimentation to use the invention commensurate in scope with the claims.

8. Claims 39-43, 50-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polypeptides having at least 80%, 85%, 90%, 95%, or 99% sequence identity with a particular disclosed sequence. The claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of polypeptides that is defined only by sequence identity.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim

is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

*Vas-Cath In. v. Mahurkar*, 19 USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for the purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to a lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO:4, but not the full breadth of the claims meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

***Claim Rejections - 35 USC § 102***

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 39-43 are rejected under 35 U.S.C. 102(a) as being anticipated by HSIEH et al. (Nature 398: 431-436, 1999).

HSIEH et al. disclose an isolated polypeptide which has 99.7% amino acid sequence identity to the amino acid sequence of the polypeptide shown in Figure 4 (SEQ ID NO:4). See Figure 1. HSIEH et al. further disclose a chimeric molecule, including a fusion with an IgG heavy-chain (see paragraph 7). Therefore, the claims are anticipated by the prior art.

11. Claims 44-49 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over HSIEH et al. (Nature 398: 431-436, 1999).

The disclosure of HSIEH et al. is as described above. The single difference in amino acid sequence between the polypeptide of SEQ ID NO:4 recited in the instant claims and the polypeptide of HSIEH et al. occurs at position 178. Specifically, the amino acid at position 178 in SEQ ID NO:4 of the instant application is glutamine, whereas the amino acid at position 178 of HSIEH et al. is leucine.

The courts have long recognized that sequencing errors can occur (*Ex parte Maizel*; 27 USPQ2d 1662, BPAI 1992, see especially pp. 1663 and 1666). The instant specification also recognizes that the sequences disclosed in the sequence listing may not be exact. At page 157 of the instant specification, it is stated that:

> "for the PRO polypeptides and encoding nucleic acids described herein, Applicants have identified what is believed to be the reading frame best identifiable with the sequence information available at the time."

Therefore, it is reasonable to expect that the single amino acid difference at position 178 of SEQ ID NO:4 of the instant application and the protein of HSIEH et al. may be the result of a sequencing error, and that the actual clones of the instant application and HSIEH et al., in fact, have identical sequences.

The Examiner is unable to determine whether the prior art disclosure actually possesses the characteristic of the sequence of SEQ ID NO:4. With these conditions, where the product seems to be identical, then the burden shifts to Applicant to provide evidence that the prior art

would neither anticipate nor render obvious the claimed invention. Note the case law of *In re Best* 195 USPQ 430, 433 (CCPA 1977).

12. Claims 39-43 are rejected under 35 U.S.C. 102(b) as being anticipated by BREWER et al. (WO 98/54963; published 10 December 1998).

BREWER et al. teach a polypeptide (SEQ ID NO:426) which has approximately 99% amino acid sequence identity with the claimed polypeptide of SEQ ID NO:4. See attached sequence alignment which references claim 11 and pages 579-580. The reference is 772 pages in length, and therefore, will not be provided in this Office action unless Applicant specifically requests the entire document. BREWER et al. further disclose a chimeric molecule, including a fusion with an IgG heavy-chain (see page 236).

13. Claims 44-49 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over BREWER et al. (WO 98/54963; published 10 December 1998).

BREWER et al. teach a polypeptide (SEQ ID NO:426) which has approximately 99% amino acid sequence identity with the claimed polypeptide of SEQ ID NO:4. See attached sequence alignment which references claim 11 and pages 579-580. The differences between the claimed polypeptide and the polypeptide of BREWER et al. are found at positions 264, 300 and 380. Positions 264 and 300 are indicated to be Xaa, which is a wildcard amino acid. Frequently in the biotech. arts, amino acid sequence analysis fails to reliably provide each and every amino acid in a protein sequence. This is sometimes due to disulfide bonds between cysteine residues.

Therefore, the amino acids at these positions may very well be cysteine residues (inherent to the polypeptide of BREWER et al), which would anticipate the instant claims since the residues at these positions in SEQ ID NO:4 are cysteine residues. With regard to inherency, where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or obviousness has been established. *In re Best*, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, *the applicant has the burden of showing that they are not* (emphasis added)." *In re Spada*, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 195 USPQ 430, 433 (CCPA 1977). In re Papesch, 315 F.2d 381, 137 USPQ 42, 51 (CCPA 1963) held that "From the standpoint of patent law, a compound and all its properties are inseparable."

In the alternative, it would have been *prima facie* obvious for one of ordinary skill in the art to place any one of the known amino acids in the recited positions of BREWER et al. since these positions were indicated to be Xaa, which could be any amino acid. The number of embodiments is relatively small, considering only two positions are indicated and it would be well within the skill of the artisan to substitute these two positions and isolate the encoded protein. It is noted that the protein of BREWER et al. has an extra amino acid at position 380, however, the instant claims recite "comprising", which encompasses additional amino acids.

***Conclusion***

14. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Christine J. Saoud, Ph.D., whose telephone number is (703) 305-7519. The Examiner can normally be reached on Monday to Friday from 7AM to 3PM. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. §§ 1.6(d) and 1.8). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 872-9306. If this number is out of service, please call the Group receptionist for an alternate number. Official papers filed After Final rejection filed by fax should be directed to (703) 872-9307.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

CHRISTINE J. SAOUD
PRIMARY EXAMINER
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